APS Search for 08/462,147
FILE 'USPAT' ENTERED AT 11:51:55 ON 18 MAR 96

=> s hyaluronic or hyaluronate or hylan or healon or hyalectin or hyalastine
923 HYALURONIC
312 HYALURONATE
20 HYLAN
109 HEALON
9 HYALECTIN
9 HYALASTINE
L1 1070 HYALURONIC OR HYALURONATE OR HYLAN OR HEALON OR HYALECTIN OR HYALASTINE

=> s antibiotic? or antibacterial? or antimicrobial? or ?infect?

20854 ANTIBIOTIC?
13049 ANTIBACTERIAL?
9788 ANTIMICROBIAL?
44866 ?INFECT?
L2 62079 ANTIBIOTIC? OR ANTIBACTERIAL? OR ANTIMICROBIAL? OR ?INFECT?

=> s l1 (p) l2
L3 102 L1 (P) L2

=> s l3 and fy<1989

1411327 FY<1989
L4 39 L3 AND FY<1989

=> d 1-39 kwic

US PAT NO: 5,204,112 [IMAGE AVAILABLE] L4: 1 of 39
DATE FILED: **Jun. 12, 1987**

DETDESC:

DETD(29)

Virtually . . . be entrapped within the liposomes for use according to the present invention. Such agents include but are not limited to **antibacterial** compounds such as gentamycin, antiviral compounds such as rifampacin, antifungal compounds such as amphotericin B, anti-parasitic compounds such as antimony. . . toxin, enzymes such as catalase, hormones such as estrogens, neurotransmitters such as acetylcholine, lipoproteins such as alpha-lipoprotein, glycoproteins such as **hyaluronic** acid, immunoglobulins such as IgG, immunomodulators such as the interferons or the interleukens, dyes such as Arsenazo III, radiolabels such. . .

US PAT NO: 5,128,321 [IMAGE AVAILABLE] L4: 2 of 39
DATE FILED: **Aug. 8, 1988**

CLAIMS:

CLMS(9)

9. The therapeutic composition of claim 8 wherein said adjuvant is selected from the group consisting of collagen, **hyaluronic** acid, fibronectin, factor XIII and an **antibiotic**.

US PAT NO: 5,098,703 [IMAGE AVAILABLE] L4: 3 of 39
DATE FILED: **Sep. 2, 1982**

DETDESC:

DETD(21)

The . . . the production of intracellular enzymes and other cell-produced substances. Accordingly, it is expected IFN-.alpha.76 may be used to treat viral **infections** with a potential for interferon therapy such as chronic hepatitis B **infection**, ocular, local, or systemic herpes virus **infections**, influenza and other respiratory tract virus **infections**, rabies and other viral zoonoses, arbovirus **infections**, and slow virus diseases such as Kuru and sclerosing panencephalitis. It may also be useful for treating viral **infections** in immunocompromised patients such as herpes zoster and varicella, cytomegalovirus, Epstein-Barr virus **infection**, herpes simplex **infections**, rubella, and progressive multifocal leukoencephalopathy. Its cell growth regulating activity makes it potentially useful for treating tumors and cancers such. . . synthetase indicates it may also increase synthesis of other enzymes or cell-produced substances commonly affected by IFNs such as histamine, **hyaluronic** acid, prostaglandin E, tRNA methylase, and aryl hydrocarbon hydrolase. Similarly, it may be useful to inhibit enzymes commonly inhibited by. . .

US PAT NO: 5,041,278 [IMAGE AVAILABLE] L4: 4 of 39
DATE FILED: **Dec. 6, 1988**

DETDESC:

DETD(27)

Compounds . . . agents can be entrapped within the alpha-tocopherol vesicles of the present invention. Such compounds include but are not limited to **antibacterial** compounds such as gentamycin, antiviral agents such as rifampacin, antifungal compounds such as amphoteracin B, anti-parasitic compounds such as antimony. . . polypeptides such as cyclosporin A, hormones such as estrogen, hormone antagonists, neurotransmitters such as acetylcholine, neurotransmitter antagonists, glycoproteins such as **hyaluronic** acid, lipoproteins such as alpha-lipoprotein, immunoglobulins such as IgG, immunomodulators such as interferon or interleuken, vasodilators, dyes such as Arsenazo. . .

US PAT NO: 5,023,175 [IMAGE AVAILABLE] L4: 5 of 39
DATE FILED: **Apr. 16, 1987**

SUMMARY:

BSUM(5)

It is now known that **hyaluronic** acid exists in every connective tissue in animal bodies. It is industrially obtained by extraction from living tissues such as fowl crests and umbilici. As its functions, **hyaluronic** acid has been reported to retain water among cells, to form gel-like matrices within cells to support the cells, to control intercellular movement of substances, and to protect cells from external physical shocks or **infection** with external bacteria, etc. Making effective use of these functions, **hyaluronic** acid is employed in pharmaceutical products (arthritic remedies, ophthalmic remedies, vulneraries, etc.), cosmetic compositions and so on.

US PAT NO: 5,012,503 [IMAGE AVAILABLE] L4: 6 of 39
DATE FILED: **Jul. 1, 1988**

SUMMARY:

BSUM(25)

As . . . polyvinyl alcohol. As the component which does not prevent gelation of polyvinyl alcohol, mention may be made of, for example, **antibiotics** such as penicillin and fradiomycin and medicines such as polymyxin B, and chondroitin sulfate, and potassium **hyaluronate**. For embedding them in hydrogel, these components as they are or as aqueous solution or suspension ca be previously added. . .

US PAT NO: 4,983,393 [IMAGE AVAILABLE] L4: 7 of 39
DATE FILED: **Oct. 14, 1988**

DETDESC:

DETD(29)

The examples listed below describe several formulations utilizing different structural components (agarose, collagen, carageenan, **hyaluronic** acid, locust bean gum) as well as different active ingredients (spermicides and **antibacterials**). The components which are used in each example are to be mixed according to the following protocol:

US PAT NO: 4,975,276 [IMAGE AVAILABLE] L4: 8 of 39
DATE FILED: **Sep. 2, 1982**

DETDESC:

DETD(20)

The . . . the production of intracellular enzymes and other cell-produced substances. Accordingly, it is expected IFN-.alpha.54 may be used to treat viral **infections** with a potential for interferon therapy such as chronic hepatitis B **infection**, ocular, local, or systemic herpes virus **infections**, influenza and other respiratory

tract virus **infections**, rabies and other viral zoonoses, arbovirus **infections**, and slow virus diseases such as Kuru and sclerosing panencephalitis. It may also be useful for treating viral **infections** in immunocompromised patients such as herpes zoster and varicella, cytomegalovirus, Epstein-Barr virus **infection**, herpes simplex **infections**, rubella, and progressive multifocal leukoencephalopathy. Its cell growth regulating activity makes it potentially useful for treating tumors and cancers such. . . synthetase indicates it may also increase synthesis of other enzymes or cell-produced substances commonly affected by IFNs such as histamine, **hyaluronic** acid, prostaglandin E, tRNA methylase, and aryl hydrocarbon hydrolase. Similarly, it may be useful to inhibit enzymes commonly inhibited by. . .

US PAT NO: 4,973,493 [IMAGE AVAILABLE] L4: 9 of 39
DATE FILED: **Oct. 15, 1987**

DETDESC:

DETD(97)

TABLE 8

Stability of Covalent Linkage to Cleaning **Disinfection** Procedures Biocompatible

Agent	Treatment	pmole/cm3	% Remaining
ANP-1000	No treatment	831	100
	Enzymatic cleaner	862	100
. . .	Enzymatic cleaner	1996	100
	Boiling	1619	98.1
	Chemical cleaner	1409	85.3
ANP- **Hyaluronate**	No treatment	300	100
	Enzymatic cleaner	317	100
	Boiling	340	100
	Chemical Cleaner	307	100

*Values are. . .

DETDESC:

DETD(98)

The covalent linkages remained 100% stable to enzymatic cleaning and thermal **disinfection**. There was some loss of biocompatible agent with the chemical **disinfection** procedures except for the ANP **hyaluronate**. 6. In Vivo Assessment of Biocompatibility.

US PAT NO: 4,973,479 [IMAGE AVAILABLE] L4: 10 of 39
DATE FILED: **Sep. 2, 1982**

DETDESC:

DETD(21)

The . . . the production of intracellular enzymes and other cell-produced substances. Accordingly, it is expected IFN-.alpha.61 may be used to treat viral **infections** with a potential for interferon therapy such as chronic hepatitis B **infection**, ocular, local, or systemic herpes virus **infections**, influenza and other respiratory tract virus **infections**, rabies and other viral zoonoses, arbovirus **infections**, and slow virus diseases such as Kuru and sclerosing panencephalitis. It may also be useful for treating viral **infections** in immunocompromised patients such as herpes zoster and varicella, cytomegalovirus, Epstein-Barr virus **infection**, herpes simplex **infections**, rubella, and progressive multifocal leukoencephalopathy. Its cell growth regulating activity makes it potentially useful for treating tumors and cancers such. . . synthetase indicates it may also increase synthesis of other enzymes or cell-produced substances commonly affected by IFNs such as histamine, **hyaluronic** acid, prostaglandin E, tRNA methylase, and aryl hydrocarbon hydrolase. Similarly, it may be useful to inhibit enzymes commonly inhibited by. . .

US PAT NO: 4,971,955 [IMAGE AVAILABLE] L4: 11 of 39
DATE FILED: **Mar. 2, 1988**

DETDESC:

DETD(75)

Chondroitin Sulfate Treatment of Aseptic Inflammation of Animal Joints

Aseptic inflammation (i.e., without **infection** by microorganisms) of the joints of animals, particularly four-legged animals such as horses, is a serious characteristic of degenerative joint disease. As the cartilage cells of the joint degenerate, the synovial fluid (which is largely **hyaluronic** acid) of the joint is of such inferior quality that it has very poor lubricating capacity (i.e., it becomes nonviscous),. . .

US PAT NO: 4,970,298 [IMAGE AVAILABLE] L4: 12 of 39
DATE FILED: **Jun. 18, 1986**

DETDESC:

DETD(1)

These . . . carrier compound wherein the carrier compound is selected from the group consisting of types IV and V collagen, fibronectin, laminin, **hyaluronic** acid, proteoglycan, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermacidal agent, enzyme and enzyme inhibitor.

DETDESC:

DETD(15)

Another . . . collagen-based matrix. Such a carrier compound is selected from the group consisting of collagen types IV and V, fibronectin, laminin, **hyaluronic** acid, proteoglycans, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermicidal agent, hormone, enzyme and enzyme inhibitor.

US PAT NO: 4,966,843 [IMAGE AVAILABLE] L4: 13 of 39
DATE FILED: **Jul. 31, 1985**

DETDESC:

DETD(69)

The . . . intracellular enzymes and other cell-produced substances. Accordingly, it is expected that IFN-.alpha.61 and IFN-.alpha.76 may be used to treat viral **infections** with a potential for interferon therapy such as chronic hepatitis B **infection**, ocular, local, or systemic herpes virus **infections**, influenza and other respiratory tract virus **infections**, rabies and other viral zoonoses, arbovirus **infections**, and slow virus diseases such as Kuru and sclerosing panencephalitis. They may also be useful for treating viral **infections** in immunocompromised patients such as herpes zoster and varicella, cytomegalovirus, Epstein-Barr virus **infection**, herpes simplex **infections**, rubella, and progressive multifocal leukoencephalopathy. Their cell growth regulating activity makes them potentially useful for treating tumors and cancers such. . . indicates that they may also increase synthesis of other enzymes or cell-produced substances commonly affected by IFNs such as histamine, **hyaluronic** acid, prostaglandin E, tRNA methylase, and aryl hydrocarbon hydrolase. Similarly, they may be useful to inhibit enzymes commonly inhibited by. . .

US PAT NO: 4,957,744 [IMAGE AVAILABLE] L4: 14 of 39
DATE FILED: **Oct. 13, 1987**

SUMMARY:

BSUM(46)

A . . . preparations used until now it has not been possible for one reason or another to obtain concentrations of therapeutically effective **antibiotics** or sulphamidics in the lachrymal secretion. This fact is fairly understandable in the case of solutions, considering the predominantly inclined. . . (3), pp. 69-72. With the esters of the present invention these difficulties can be overcome. Indeed, the presence of the **hyaluronic** ester as a vehicle in ophthalmic drugs allows for the formulation of excellent preparations with no concentration gradient of active. . . effect. Medicaments containing the new derivatives which may be used in ophthalmic treatments mainly

concern miotic, wound healing, anti-inflammatory and anti-microbial/**antibiotic** effects. Some examples of **antibiotic** substances are: basic and nonbasic **antibiotics**, for example aminoglucosidics, macrolidics, tetracycline and peptides, such as for example gentamycin, neomycin, streptomycin, dihydrostreptomycin, kanamycin, amikacin, tobramycin, spectinomycin, erythromycin,. . .

SUMMARY:

BSUM(50)

The . . . invention. Such solutions are preferably in distilled water or sterile saline and contain prefereably no other pharmaceutical vehicle besides the **hyaluronic** ester or one of its salts. The concentrations of such solutions may also vary within wide limits, for example between. . . solutions or diluted in water or saline, possibly with the addition of additive or auxilliary substances, such as in particular **disinfectant** substances or mineral salts acting as vehicle or others, for ophthalmic use.

DETDESC:

DETD(294)

The cosmetic articles may, however, be based on substances with specific actions which differ from those of **hyaluronic** acid, for example **disinfectants**, sunshields, waterproofing or regenerating substances, or anti-wrinkle or odoriferous substances, especially perfumes. In this case the new cross-linked derivatives of. . .

US PAT NO: 4,909,942 [IMAGE AVAILABLE] L4: 15 of 39
DATE FILED: **Oct. 12, 1988**

DETDESC:

DETD(20)

Any . . . efficiently adsorb pyrogens. Preferably examples thereof include those obtained by immobilizing, for example, an amino acid, iminodiacetic acid or an **antibiotic** on a substrate comprising, for example, agarose or cellulose. Alternately, an adsorbent obtained by binding a nitrogenous heterocyclic compound such as L-histidine to a water-insoluble carrier (cf. Japanese Patent Laid-Open No. 183172/1982) or another one comprising **hyaluronic** acid and an anionic resin (cf. Japanese Patent Laid-Open No. 67024/1979).

US PAT NO: 4,889,919 [IMAGE AVAILABLE] L4: 16 of 39
DATE FILED: **Dec. 15, 1986**

CLAIMS:

CLMS(13)

13. The composition of claim 12 wherein said adjuvant is selected from the group consisting of collagen, **hyaluronic** acid, fibronection, factor XIII, and an **antibiotic**.

US PAT NO: 4,885,172 [IMAGE AVAILABLE] L4: 17 of 39
DATE FILED: **Dec. 15, 1986**

DETDESC:

DETD(9)

Compounds . . . bioactive agents can be entrapped within the liposomes of the present invention. Such compounds include but are not limited to **antibacterial** compounds such as gentamycin, antiviral agents such as rifampacin, antifungal compounds such as amphotericin B, anti-parasitic compounds such as antimony. . . polypeptides such as cyclosporin A, hormones such as estrogen, hormone antagonists, neurotransmitters such as acetylcholine, neurotransmitter antagonists, glycoproteins such as **hyaluronic** acid, lipoproteins such as alpha-lipoprotein, immunoglobulins such as IgG, immunomodulators such as interferon or interleuken, vasodilators, dyes such as Arsenazo. . .

US PAT NO: 4,865,601 [IMAGE AVAILABLE] L4: 18 of 39
DATE FILED: **Jul. 7, 1987**

DETDESC:

DETD(52)

Once . . . for example an acetylcholine solution, the anterior chamber washed using for example a 0.9% sterile saline solution and reformed using **healon**, and the incision may be sutured closed using a suitable filament such as for example a 9-0 nylon. An **antibiotic** solution is administered under the conjunctiva for purpose of prophylaxis, for example gentamicin being used for that purpose.

US PAT NO: 4,861,580 [IMAGE AVAILABLE] L4: 19 of 39
DATE FILED: **Sep. 24, 1986**

DETDESC:

DETD(26)

Compounds . . . agents can be entrapped within the alpha-tocopherol vesicles of the present invention. Such compounds include but are not limited to **antibacterial** compounds such as gentamycin, antiviral agents such as rifampacin, antifungal compounds such as amphoteracin B, anti-parasitic compounds such as antimony. . . polypeptides such as cyclosporin A, hormones such as estrogen, hormone antagonists, neurotransmitters such as acetylcholine, neurotransmitter antagonists, glycoproteins such as **hyaluronic** acid, lipoproteins such as alpha-lipoprotein, immunoglobulins such as IgG, immunomodulators such as interferon or interleuken, vasodilators, dyes such as Arsenazo. . .

US PAT NO: 4,851,521 [IMAGE AVAILABLE] L4: 20 of 39
DATE FILED: **Jul. 2, 1986**

SUMMARY:

BSUM(37)

As discussed above, in some cases **hyaluronic** acid esters may be of interest where the ester groups derive from two or more therapeutically active hydroxylic substances, and. . . example with the same or similar activity as that of the esterifying component. In particular, it is possible to have **hyaluronic** esters deriving on the one hand from an antiinflammatory steroid, such as one of those mentioned previously, and on the other hand from a vitamin, from an alkaloid or from an **antibiotic**, such as one of those listed.

SUMMARY:

BSUM(58)

The use of **hyaluronic** esters as a vehicle allows therefore the preparation of the new medicaments described above, including (1) a pharmacologically active substance or an association of two or more of such substances and (2) a **hyaluronic** ester as described above or one of its salts, and such medicaments are a further object of the invention. In. . . ammonium. Should the active substance component (1) or a corresponding association of substances have basic groups, such as for example **antibiotics** containing amine groups, and if partial esters of **hyaluronic** acid should be used with remaining free carboxylic groups, the corresponding salts are formed between the carboxylic groups and these basic substances. The new medicaments therefore include in particular partial esters of **hyaluronic** acid partially and totally salified with pharmacologically active substances and of a basic character. As described above, particularly important are. . .

SUMMARY:

BSUM(66)

The vehicling action of the **hyaluronic** esters also applies to associated medicaments of the type mentioned above in which the active substance acts not only topically. . . mentioned, in practically all sectors of medicine, such as internal medicine, for example in pathologies of the cardiovascular system, in **infections** of the respiratory system, the digestive system, the renal system, in diseases of an endocrinological nature, in oncology, in psychiatry. . .

SUMMARY:

BSUM(79)

If . . . substances are used, such as those mentioned above, the salts of the basic active substances and the partial ester of **hyaluronic** acid may be mixed salts of one or more of such basic substances or possibly mixed salts of this type. . . salified with

metals or bases mentioned above. For example, it is possible to prepare salts of a partial ester of **hyaluronic** acid or of one of the molecular fractions **Hyalastine** or **Hyalectin** with a pharmacologically inactive alcohol, for example a lower alkanol and with a certain percentage of salified acid groups with the **antibiotic** kanamycin, another percentage of carboxylic groups salified with the vasoconstrictor phenylephrine, and a remaining percentage of acid groups may be,. . . one of the other above mentioned metals. It is also possible to mix this type of mixed salt with free **hyaluronic** acid or its fractions or their metallic salts, as indicated above for the medicaments containing salts of one single active. . .

DETDESC:

DETD(316)

The cosmetic articles may however be based on substances with specific actions other than those of **hyaluronic** acid, for example **disinfectant** substances, sunshields, waterproofing or regenerating or antiwrinkle substances, or odorants, especially perfumes. In this case the **hyaluronic** ester may itself be the active ingredient and derives from alcohols with the same properties, for example from higher aliphatic. . .

US PAT NO: 4,846,172 [IMAGE AVAILABLE] L4: 21 of 39
DATE FILED: **May 26, 1987**

DETDESC:

DETD(5)

In . . . of the irido-corneal angle 40. The anterior chamber depth is maintained by the aspiration/infusion probe device B and/or by sodium **hyaluronate** (**Healon**) following the paracentesis opposite the proposed filter site. The flexible fiberoptic element B, mounted on the end of a handpiece. . . and the sub-Tenon's space 37 and possibly also the Canal of Schlemmm 35. Withdrawal of the fiber probe B permits **Healon** from the anterior chamber 10 to access the sub-Tenon space 37, dissecting a filtration bed and creating a bleb. The fiber B is then entirely removed and topical **antibiotic**/steroid drops instilled.

US PAT NO: 4,841,962 [IMAGE AVAILABLE] L4: 22 of 39
DATE FILED: **Sep. 11, 1987**

SUMMARY:

BSUM(13)

Another . . . and subsequently delivered to the wound site which affect cell growth, such as collagen types IV and V, fibronectin, laminin, **hyaluronic** acid, and proteoglycans. Similarly, pharmacologically active agents such as epidermal growth factor, platelet derived growth factor, transforming growth factor beta, angiogenesis factor, **antibiotics**, antifungals, spermicidals, hormones, enzymes, and/or enzyme inhibitors can also be incorporated into the collagen matrix.

US PAT NO: 4,840,941 [IMAGE AVAILABLE] L4: 23 of 39
DATE FILED: **Jan. 15, 1988**

DETDESC:

DETD(105)

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	Molecular S-content	**Infected** cell (%)*		
Test substance	weight (%)	10 .mu.g/ml	100 .mu.g/ml	1000 .mu.g/ml

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-
-
(1) Dextrans, their synthetic sulfates, and. . .
Heprin 7,000-3,000
13 41 1
Heparitin sulfate
15,000 7 100 90
Keratan sulfate 4,000-20,000
7 100 60
Hyaluronic acid 10,000-100,000
0 100 100
Hyaluronic acid sulfate 8 100 70

-
-
*The control without test substance shows the value of 100% as the **infected** cell rate under the same conditions.

US PAT NO: 4,820,516 [IMAGE AVAILABLE] L4: 24 of 39
DATE FILED: **Feb. 14, 1986**

DETDESC:

DETD(28)

6. As an **antibiotic** to remove or weaken the **hyaluronic** acid capsule surrounding certain pathogenic microorganisms, such as Streptococcus-associated periodontal diseas and streptococcal pneumonia; and as an adjunct in such cases to other **antibiotics** directed towards the same microorganisms.

US PAT NO: 4,784,991 [IMAGE AVAILABLE] L4: 25 of 39
TITLE: Heavy metal salts of **hyaluronic** acid and their use as **antimicrobial** agents
DATE FILED: **Mar. 9, 1987**

ABSTRACT:
Heavy metal salts of **hyaluronic** acid have been prepared. In particular, this invention is directed to silver, gold, cerium and tungsten salts of **hyaluronic** acid. These heavy metal salts of **hyaluronic** acid are useful as **antimicrobial** agents. Gold **hyaluronate** may also be used to treat arthritis.
This invention also concerns methods of making the silver salt of hyaluronic acid as. . .

SUMMARY:

BSUM(16)

The present invention concerns methods of producing silver **hyaluronate**, compositions containing silver **hyaluronate**, and the treatment of wounds, burns and **infections**, especially soft-tissue **infections** and gonoccocal ophthalmalogical **infections**, with silver **hyaluronate**.

SUMMARY:

BSUM(17)

The invention further concerns a method for treating keratitis with silver **hyaluronate** and optionally in conjunction with **antibiotics**.

SUMMARY:

BSUM(25)

These heavy metal salts of **hyaluronic** acid are useful as **antimicrobial** agents. In particular, microbial growth may be inhibited by contacting the microbes with an effective amount of silver **hyaluronate**. Silver **hyaluronate** may also be used to inhibit microbial growth in **infections**, by topically applying an effective amount of the silver **hyaluronate** to the **infection**.

DETDESC:

DETD(7)

The heavy metal salts of **hyaluronic** acid and compositions d containing same are useful as **antimicrobial** agents. In particular, microbial growth may be inhibited by contacting the microbes with an effective amount of silver **hyaluronate**. Silver **hyaluronate** may also be used for treating burns, wounds, soft tissue **infections**, for example, gonoccocal opthalmalogical **infections** or sepsis by topically applying an effective amount of the silver **hyaluronate** to the site of the burn, wound, soft tissue **infection** or **infection** from which the sepsis stems. Silver **hyaluronate** compositions are also used for

treating keratitis **infections**.

DETDESC:

DETD(56)

ANTIMICROBIAL ACTIVITY OF SILVER **HYALURONATE**

DETDESC:

DETD(92)

USE OF SILVER **HYALURONATE** AGAINST PSEUDOMONAS AERUGINOSA
INFECTION IN A RABBIT EYE MODEL

DETDESC:

DETD(94)

Keratitis produced by Pseudomonas aeruginosa is the most rapidly spreading and destructive bacterial disease with which the human cornea can be **infected**, as well as the most disastrous (Laibson, 1972). The frequency of corneal **infections** has greatly increased with the use of contact lens. Treatment of early-detected pseudomonas **infections** with aminoglycosidic **antibiotics** such as gentamycin usually results in a good therapeutic response. However, the increasing occurrence of **antibiotic**-resistant bacteria presents a problem, which becomes disastrous when such a situation is detected post-factum. The use of an efficient wide range anti-bacterial agent, such as silver **hyaluronate**, might overcome this problem.

DETDESC:

DETD(103)

Initial studies were performed with 0.5% w/v of silver **hyaluronate** in water prepared as described in Example 1. This solution is quite viscous, but its viscosity does not interfere with. . . was found that at this concentration the treated eyes developed a marked irritation of the conjunctive, irrespective of the bacterial **infection**. Hence, the 0.5% AgHA solution was diluted three-fold with 0.5% NaHA aqueous solution (final AgHA concentration 0.17%). A slight irritation. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of treating a subject having keratitis which method comprises topically applying to an **infection** causing the keratitis an effective amount of a silver salt of **hyaluronic** acid.

CLAIMS:

CLMS(2)

2. A method of claim 1, wherein an **antibiotic** is used in conjunction with the silver salt of **hyaluronic** acid.

US PAT NO: 4,782,046 [IMAGE AVAILABLE] L4: 26 of 39
DATE FILED: **Sep. 18, 1986**

DETDESC:

DETD(10)

In . . . 24 hours to 120 hours at 37.degree. C. A special chemically defined media, described by I. van de Rijn in **Infect**. and Immun., 27:444-448, 1980, was used for growth. This media is preferable since it contains no extraneous proteins which would. . . drop to 6.5 to 6.8 where the culture stops growing. This allows more efficient centrifugation and somewhat better yields of **hyaluronic** acid.

US PAT NO: 4,746,504 [IMAGE AVAILABLE] L4: 27 of 39
TITLE: Heavy metal salts of **hyaluronic** acid and their use as **antimicrobial** agents
DATE FILED: **Mar. 14, 1986**

ABSTRACT:

Heavy metal salts of **hyaluronic** acid have been prepared. In particular, this invention is directed to silver, gold, cerium and tungsten salts of **hyaluronic** acid. These heavy metal salts of **hyaluronic** acid are useful as **antimicrobial** agents. Gold **hyaluronate** may also be used to treat arthritis. This invention also concerns methods of making the silver salt of **hyaluronic** acid as well as compositions containing silver **hyaluronate** or gold **hyaluronate**. The invention also concerns composition containing heavy metal salts having radioactively labelled **hyaluronate** moieties.

SUMMARY:

BSUM(16)

The present invention concerns methods of producing silver **hyaluronate**, compositions containing silver **hyaluronate**, and the treatment of wounds, burns and **infections**, especially soft-tissue **infections** and gonoccocal opthalmalogical **infections**, with silver **hyaluronate**.

SUMMARY:

BSUM(23)

These heavy metal salts of **hyaluronic** acid are useful as **antimicrobial** agents. In particular, microbial growth may be inhibited by contacting the microbes with an effective amount of silver **hyaluronate**. Silver **hyaluronate** may also be used to inhibit microbial growth in **infections**, by topically applying an effective amount of the silver **hyaluronate** to the **infection**.

DETDESC:

DETD(8)

The heavy metal salts of **hyaluronic** acid and compositions containing same are useful as **antimicrobial** agents. In particular, microbial growth may be inhibited by contacting the microbes with an effective amount of silver **hyaluronate**. Silver **hyaluronate** may also be used for treating burns, wounds, soft tissue **infections**, for example, gonoccocal opthalmalogical **infections** or sepsis by topically applying an effective amount of the silver **hyaluronate** to the site of the burn, wound, soft tissue **infection** or **infection** from which the sepsis stems.

DETDESC:

DETD(56)

Antimicrobial Activity of Silver **Hyaluronate**

DETDESC:

DETD(61)

Antimicrobial Activity of Ag-**hyaluronate**

US PAT NO: 4,736,024 [IMAGE AVAILABLE] L4: 28 of 39
DATE FILED: **Apr. 3, 1986**

SUMMARY:

BSUM(46)

One particular form of medicament according to the invention is represented by mixtures of the pharmacologically active substance Component (1) with **hyaluronic** acids or molecular fractions thereof when the said active substance (1) is of a basic nature, for example in the case of basic **antibiotics**. In this case, the **hyaluronic** acid component (2) and the active substance (1) together from stoichiometrically partial salts, or acid salts, in which an aliquot. . .

SUMMARY:

BSUM(48)

Mixtures . . . (1), mixtures of active substances are used, such as those mentioned above, the salts of the basic active substances and **hyaluronic** acid and its molecular weight fractions may be mixed salts of one or more of such basic substances or possibly. . . the HY

polysaccharide salified with the above mentioned metals or bases. For example, it is possible to prepare salts of **hyaluronic** acid or one of the molecular fractions **Hyalastine** or **Hyalectin** with a certain percentage of salified acid groups with the **antibiotic** kanamycin, another percentage salified with the vasocostrictor phenylephrine, while a remaining percentage acid groups are free or salified for example. . . . of the above mentioned metals. It is also possible to mix this type of mixed salt with other quantities of **hyaluronic** acid or its fractions or their metallic salts, as indicated above for the medicament containing salts of only one active. . .

SUMMARY:

BSUM(52)

In . . . present invention. Such solutions are preferably in distilled water or sterile saline and contain preferalby no other pharmaceutical vehicle besides **hyaluronic** acid or one of its salts. The concentrations of such solutions may also vary within ample limits, for example between. . . concentrated solutions or diluted in water or saline, possibly with the addition of additive or auxiliary substances, such as particular **disinfectant** substances or mineral salts acting as buffer or others, for ophthalmic use.

DETDESC:

DETD(169)

The . . . use of component (1) when administered in a conventional way. As an example, hereinafter are reported experiments carried out with **hyaluronic** acid salts with the following **antibiotics**: streptomycin, erythromycin, neomycin, gentamicin. These are the total salts in which all of the acid groups of **hyaluronic** acid are salified with a basic group of the **antibiotic**, and are described in examples 1, 2, 4 and 5. Of these, solutions in distilled water were used, having concentrations suitable to the **antibiotic** content, as follows:

DETDESC:

DETD(176)

The . . . the present invention was followed by a more rapid recovery from inflammation as compared to the administration of the corresponding **antibiotics** not salified with **hyaluronic** acid.

DETDESC:

DETD(295)

ANTIMICROBIAL ACTIVITY OF GENTAMICIN VEHICLED IN **HYALURONIC** ACID

DETDESC:

DETD(301)

Septic . . . 11 rabbits by intraocular injection of a titered suspension of pseudomonas aeruginosa (0.1 ml). In those rabbits showing septic inflammation, **hyaluronic** acid **HYALECTIN** fraction in combination with gentamicin was administered by instillation in the right eye, and gentamicin in a phosphate saline vehicle. . . was administered in the left eye. The treatment (3 drops every 6 hours) was begun immediately after injection of the **infective** agent and was continued until disappearance of the **infection**. The eyes of the rabbits were observed every dat with a slit lamp.

DETDESC:

DETD(303)

Treatment with a combination of gentamicin and **hyaluronic** acid resulted in the more rapid disappearance of septic **infection** when compared to the administration of the **antibiotic** alone. This conclusion is clear from the data reported in Table 7.

US PAT NO: 4,725,585 [IMAGE AVAILABLE] L4: 29 of 39
DATE FILED: **Sep. 20, 1985**

DETDESC:

DETD(1)

The . . . described more in detail in the following nonlimiting examples relating to the treatment of a plurality of patients having increased **infection** propensity with **hyaluronic** acid in accordance with the present invention. The preparation used in these Examples was **Healon**.RTM., provided by Pharmacia AB, Uppsala, Sweden. This preparation was an aqueous sterile solution for injection, 1 ml of which containing:

DETDESC:

DETD(13)

Development . . . to bed, but the fever periods declined somewhat. The treatment was continued during the summer and she became substantiallyfree from **infections**, could be mobilized and had been at home. The treatment was continued until Oct. 1, 1978, when the patient herself. . . treatment. The patient was once again hospitalized at the University Hospital, the phagocytosis function was evaluated and the treatment with **hyaluronic** acid was started again. About 10 days after the first injection the fever periods of the patient were once again. . .

DETDESC:

DETD(16)

Conclusion. This is a very ill patient with a long and serious **infection** anamnesis and confinement to bed for almost 1 year due to serious **infections**. In connection with the treatment with **hyaluronic** acid the patient could be mobilized and became free of fever. When the treatment was interrupted the fever periods returned. Resumption of treatment with **hyaluronic** acid resulted in an improvement in the patient's function subjectively and objectively.

DETDESC:

DETD(22)

Development . . . The patient was operated on Dec. 18, 1978 for the valve defect, and the post-operative development was completely free from **infections**. The patient returned to the hospital Mar. 5, 1979 since he had again had a bacterial **infection**, this time a sinusitis. By experience the patient's **infections** have been hard to treat, and the patient was therefore once again given **hyaluronic** acid in combination with an **antibiotic**. The condition of the patient was rapidly improved.

DETDESC:

DETD(25)

Conclusion. This is an abnormally **infectionprone** individual, who has been tested by us several times during the last years. Because of the severe heart valve defect it was considered vital to operate on the patient. **Hyaluronic** acid was given in order to prevent the possible development of **infections** in the post-operative stage. The patient had no post-operative complications.

DETDESC:

DETD(34)

Conclusion. . . . emphysema development and a pessimistic prognosis quo ad vitam has been treated for a little more than one month with **hyaluronic** acid, and she has during this period experienced a clear improvement with regard to the number of **infection** episodes.

DETDESC:

DETD(60)

Conclusion. The patient had an average size skin burn and **infection** complication in the wound areas. He initially had a very poor general condition and a poor phagocytosis function. Both parts were improved in connection with the treatment with **hyaluronic** acid.

CLAIMS:

CLMS(3)

3. A method for treating or preventing **infections** associated with reduced phagocytic activity, in mammals, comprising administering subcutaneously or intramuscularly to a mammal a therapeutically effective amount of a non-antigenic **hyaluronic** acid preparation containing **hyaluronic** acid or a physiologically acceptable salt thereof.

CLAIMS:

CLMS(9)

9. A method for treating **infections** in humans associated with reduced phagocytic activity, comprising administering subcutaneously or intramuscularly to a human a therapeutically effective amount of a non-antigenic **hyaluronic** acid or a physiologically acceptable salt thereof.

US PAT NO: 4,703,108 [IMAGE AVAILABLE] L4: 30 of 39
DATE FILED: **Mar. 26, 1986**

ABSTRACT:
There . . . carrier compound wherein the carrier compound is selected from the group consisting of types IV and V collagen, fibronectin, laminin, **hyaluronate**, proteoglycan, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermacidal agent, enzyme and enzyme inhibitor.

SUMMARY:

BSUM(19)

These . . . carrier compound wherein the carrier compound is selected from the group consisting of types IV and V collagen, fibronectin, laminin, **hyaluronate**, proteoglycan, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermacidal agent, enzyme and enzyme inhibitor.

SUMMARY:

BSUM(31)

Another . . . collagen-based matrix. Such a carrier compound is selected from the group consisting of collagen types IV and V, fibronectin, laminin, **hyaluronate**, proteoglycans, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermacidal agent, hormone, enzyme and enzyme inhibitor.

CLAIMS:

CLMS(19)

19. The cross-linked matrix of claim 11 which further includes a compound selected from the group consisting of **hyaluronate**, fibronectin, laminin, proteoglycan, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermicidal agent, enzyme and enzyme inhibitor, wherein the compound is cross-linked within the matrix.

CLAIMS:

CLMS(31)

31. . . . carbodiimide and dehydrothermal cross-linked collagen matrix which consists essentially of collagen and a compound selected from the group consisting of **hyaluronate** fibronectin, laminin, proteglycan, epidermal growth factor, platelet derived growth factor, angiogenesis factor, **antibiotic**, antifungal agent, spermicidal agent, enzyme and enzyme inhibitor, wherein the compound is cross-linked within the matrix, which matrix promotes fibroblast. . .

US PAT NO: 4,695,536 [IMAGE AVAILABLE] L4: 31 of 39
DATE FILED: **Jan. 10, 1984**

CLAIMS:

CLMS(2)

2. . . .
25 mM HEPES buffer without L-glutamine, 5 ml of L-glutamine at 1 percent final concentration of final media volume and **antibiotics** including 50-100 ug/ml of garamycin sulfate;
b. an effective amount of serum from the group of calf serum, fetal calf serum. . . corneal preservation, and;
c. an effective amount of a high molecular weight compound selected from the group of chondroitin sulfate, sodium **hyaluronate**, heparan sulfate, keratan sulfate, dextran or cellulose gum, for maintaining corneal deturgescence during immediate and long term preservation.

CLAIMS:

CLMS(7)

7. . . .
HEPES buffer without L-glutamine, 5 ml of L-glutamine (200 mM) at 1 percent final concentration of final media volume and **antibiotics** including 50-100 ug/ml of garamycin; serum from the group of calf serum, fetal calf serum or human serum; and an effective amount of high molecular weight molecule selected from a group consisting of chondroitin sulfate, sodium **hyaluronate**, keratan sulfate, sodium **hyaluronate**, keratan sulfate, polyvinyl-pyrolidone, methyl cellulose, hydroxy-prophylmethylcellulose, cellulose gum and dextran;
b. filling a corneal storage container with said mixed media; and,
c.. . .

US PAT NO: 4,670,257 [IMAGE AVAILABLE] L4: 32 of 39
DATE FILED: **Feb. 19, 1985**

SUMMARY:

BSUM(14)

The . . . cited in Chemical Abstracts Vol. 55, No. 5 (Mar. 6, 1961) No. 4892c describe the preparation of a product containing **hyaluronic** acid by extraction from the vitreous humour of cattle eyes, and its application to the treatment of **infected** wounds. The product is a chloroformic extract.

US PAT NO: 4,657,901 [IMAGE AVAILABLE] L4: 33 of 39
DATE FILED: **Sep. 7, 1984**

SUMMARY:

BSUM(14)

As the sebum secretion depressant, there may be mentioned hormones of the female type such as estradiol. Examples of the **antimicrobial** agents include hexachlorophene, trichlorocarbanilide, benzalkonium chloride, phenol, cetyl pyridinium chloride, undecylenic acid and bithionol. As the surface active agent, there. . . potassium lauroate, potassium stearate), etc. Examples of the astringents include tannin and so forth. Examples of the humidifying agents include **hyaluronic** acid, sodium **hyaluronate**, chondroitin sulfate, pyrrolidonecarboxylic acid, sodium pyrrolidonecarboxylate and so forth. As the pH adjusting agent, there may be mentioned acids and. . .

US PAT NO: 4,533,635 [IMAGE AVAILABLE] L4: 34 of 39
DATE FILED: **Feb. 18, 1981**

SUMMARY:

BSUM(10)

The . . . cited in Chemical Abstracts Vol. 55, No. 5 (Mar. 6, 1961) No. 4892c describe the preparation of a product containing **hyaluronic** acid by extraction from the vitreous humour of cattle eyes, and its application to the treatment of **infected** wounds. The product is a chloroformic extract.

US PAT NO: 4,477,435 [IMAGE AVAILABLE] L4: 35 of 39
DATE FILED: **Sep. 30, 1982**

SUMMARY:

BSUM(9)

The . . . cited in Chemical Abstracts Vol. 55, no 5 (Mar. 6, 1961) no. 4892c describe the preparation of a product containing **hyaluronic** acid by extraction from the vitreous humor of cattle eyes, and its application to the treatment of **infected** wounds. The product is a chloroformic extract.

US PAT NO: 4,328,803 [IMAGE AVAILABLE] L4: 36 of 39

DATE FILED: **Oct. 20, 1980**

DETDESC:

DETD(20)

This . . . employed in Example II. The only departure from the method described in Example II was that the 1.0 wt. % "**HEALON**" was diluted at the surgical site at the close of the surgical procedure. This was accomplished by irrigating the anterior. . . of the anterior chamber. It was thereby possible to effect a dilution of the 1.0 wt. % concentration of sodium **hyaluronate** at the surgical site. Using this technique, the "**HEALON**" concentration was reduced in the anterior chamber at the close of the procedure to approximately the 0.1 to 0.3 wt.. . . of 10-0 Nylon material. Following this, the conjunctival flap was also closed, using two interrupted sutures of 6-0 plain gut. **Antibiotic** and cortiscosteroid ointment was placed in the eye and a sterile patch put in place. The patient was taken from. . .

US PAT NO: 4,258,134 [IMAGE AVAILABLE] L4: 37 of 39
DATE FILED: **May 3, 1979**

SUMMARY:

BSUM(2)

It . . . noted that "Hyaluronidase" is a general term for an enzyme, which is, in common, capable of cleavaging glucosidic bonds of **hyaluronic** acid and, to a variable degree, of some other acid mucopolysaccharides of connective tissue. As to the utility of hyaluronidase,. . . and has been used as a spreading agent to promote diffusion and hasten absorption in medical use and used in **antibiotic** solution for the treatment of animal disease, e.g. bovine mastitis in veterinary use (cf. The Merck Index, Eighth Edition), and. . .

US PAT NO: 3,983,003 [IMAGE AVAILABLE] L4: 38 of 39
DATE FILED: **Jan. 20, 1976**

ABSTRACT:
A **hyaluronic** acid-enriched mycobacteria culture medium whose base is either Dubos oleic acid-albumin liquid medium or a physiological mixture of fresh yeast. . . extract in a phosphate buffer of pH 5.5 to 7 optionally containing bovine serum albumin, glycerine, a contaminating organism-growth inhibitory **antibiotic**, and a gelatinizing agent to solidify the culture medium for plate use. The culture medium has particular utility for the. . .

SUMMARY:

BSUM(11)

The above and other objects are achieved in accordance with the present invention by providing a **hyaluronic** acid-enriched mycobacteria culture medium whose base is selected from the group consisting of (a) a physiological mixture comprising fresh yeast. . . weight in a phosphate buffer of pH 5.5 to 7 and (b) Dubos oleic acid-albumin liquid medium. The amount of **hyaluronic** acid present in such culture medium sufficient to promote growth of leprosy mycobacteria is on the order of at least. . . about 0.1% by weight. The fresh yeast extract-containing culture medium base also preferably contains bovine serum albumin, glycerin and an **antibiotic** in an amount effective to inhibit growth of contaminating organisms, and may be used either in liquid form or solidified. . .

SUMMARY:

BSUM(14)

In one of the embodiments of the present invention, the mycobacteria culture medium is a **hyaluronic** acid-enriched culture medium whose base is a physiological mixture comprising about 70 to 90% by weight of a phosphate buffer. . . yeast extract, 0 to 10% by weight of bovine serum albumin, and 0 to 5% by weight of glycerin. The **hyaluronic** acid is incorporated in the culture medium in amounts sufficient to promote growth of the mycobacterium to be cultivated therein,. . . which is generally on the order of at least about 0.1% by weight. The culture medium also preferably contains an **antibiotic** in an amount effective to inhibit growth of contaminating organisms. An **antibiotic** found particularly suitable for this purpose, for example, is potassium penicillin G, available from Eli Lilly and Co. in the. . .

SUMMARY:

BSUM(18)

The above-described culture medium may suitably be prepared by forming a first solution by mixing the glycerin and the **hyaluronic** acid with a portion of the phosphate buffer and autoclaving, for example, at 15 psi for 15 minutes; and forming. . . buffer. These two solutions can then be combined, followed by the addition thereto of the fresh yeast extract and the **antibiotic**. The whole medium can then be filtered, for example, by passing it through a Seitz filter, and thereafter refrigerated until. . .

US PAT NO: 3,793,151 [IMAGE AVAILABLE] L4: 39 of 39
DATE FILED: **Jul. 10, 1972**

SUMMARY:

BSUM(3)

Streptococcus zooepidemicus and Streptococcus pyogenes, members of the Pyogenic group of Streptococci, both produce a capsular structure composed of **hyaluronic** acid at the outer surface of their cell walls. This capsule has been implicated in the virulence of the latter. . . Exp. Med., 110: 603-605 (1959); Rothbard, J. Exp. Med. 88: 325 (1948); Kass and Seastone, "The Role of Mucoid Polysaccaride (**hyaluronic** acid) in the Virulence of Group A Hemolytic Streptococci," J. Exp. Med., 79: 319-329 (1944). Such encapsulated cells are also resistant to **infection** and lysis by bacteriophage, hereinafter referred to as "phage."

SUMMARY:

BSUM(4)

It has been found that a strain of S. pyogenes which produces a **hyaluronic** acid capsule, a phage specific for this strain, and an appropriate positive control, which in this case is the enzyme. . . which inhibit the synthesis of said capsule. Such substances, hereinafter referred to as anticapsular compounds, do not usually exhibit classical **antibacterial** activity, and thus are not detected in conventional **antibiotic** screens currently employed by those skilled in the art.

SUMMARY:

BSUM(5)

The anticapsular compounds detected in the screening process of this invention inhibit the synthesis of the **hyaluronic** acid capsule of S. pyogenes. Cells of S. pyogenes thus treated are significantly more susceptible than encapulated cells to in. . . human leukocytes. Administering anticapsular compounds to a suitable host may allow the host's phagocytic system to more readily destroy the **infecting** S. pyogenes, as well as enhance the activity of conventional **antibiotics** against such organisms. Such compounds may also be useful in treating conditions in man wherein an increased production of **hyaluronic** acid is implicated. Such conditions include Marfan's syndrome, Hurler's syndrome, myxedema, osteroarthritis, arthro-acteoonychodysplasia, and neuropathy.

SUMMARY:

BSUM(8)

Generally . . . solutions of organic compounds are screened for anticapsular activity as follows. Assay plates are prepared containing a culture of the **hyaluronic** acid capsule-forming Streptococcus, and a stock solution of the particular bacteriophage which will **infect** and lyse the organism only when the organism is not encapsulated. Control plates contain no bacteriophage. Filter paper discs, dipped. . . recorded after a suitable incubation period. Samples producing zones of inhibition on the control plates are considered to exhibit classical **antibiotic** activity and are discarded. Samples producing zones of lysis on test plates, but no zones of growth inhibition on control. . .

CLAIMS:

CLMS(1)

1. A method of screening for compounds which inhibit the formation of

hyaluronic acid capsules on pathogenic microorganisms comprising:

a. selecting a **hyaluronic** acid capsule-forming microorganism, a bacteriophage which will **infect** and lyse the microorganism only when said microorganism is non-encapsulated, and a positive control which is an amount of hyaluronidase which will remove the **hyaluronic** acid capsule formed by said microorganism without destroying the microorganism, or bacteriophage;

b. plating the **hyaluronic** acid capsule-forming microorganism and a bacteriophage on the agar test plate;

c. plating said **hyaluronic** acid capsule-forming microorganism on an agar control plate;

d. applying a compound to be tested to an area of said test. .